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Anti-leprosy drug clofazimine inhibits growth of triple-negative breast cancer cells via inhibition of canonical Wnt signaling

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ABSTRACT

Research on existing drugs often discovers novel mechanisms of their action and leads to the expansion of their therapeutic scope and subsequent remarketing. The Wnt signaling pathway is of the immediate therapeutic relevance, as it plays critical roles in cancer development and progression. However, drugs which disrupt this pathway are unavailable despite the high demand. Here we report an attempt to identify antagonists of the Wnt–FZD interaction among the library of the FDA-approved drugs. We performed an *in silico* screening which brought up several potential antagonists of the ligand-receptor interaction. 14 of these substances were tested using the TopFlash luciferase reporter assay and four of them identified as active and specific inhibitors of the Wnt3a-induced signaling. However, further analysis through GTP-binding and β-catenin stabilization assays showed that the compounds do not target the Wnt-FZD pair, but inhibit the signaling at downstream levels. We further describe the previously unknown inhibitory activity of an anti-leprosy drug clofazimine in the Wnt pathway and provide data demonstrating its efficiency in suppressing growth of Wnt-dependent triple-negative breast cancer cells. These data provide a basis for further investigations of the efficiency of clofazimine in treatment of Wnt-dependent cancers.

1. Introduction

Despite multiple efforts in development of novel therapies, bringing novel drugs to the market is a costly and time-consuming process that is coupled with great risks of failure. In many cases the candidate substance does not reach the patients due to its side effects, which are in turn the product of the off–target interactions. Virtually any small molecule has at least several interactors among tens of thousands of macromolecules present in our bodies. Normally undesirable, such interactions of approved drugs with known toxicity profiles are sometimes of a potential great value as they might be useful for treatment of other diseases, resulting in quick and low-cost repositioning of the drug. Consequently, many researchers are searching for novel applications of substances that have already passed the filter of clinical trials. To-date these efforts resulted in the "second life" of 22 drugs [1]. In many cases novel fields of drug application are unexpected, such as the notorious case of sildanefil (Viagra) [2] promoted from a poor remedy against hypertension and angina to the rescue for erectile dysfunction; or a less known case of thalidomide, leaping from the dangerous (and later prohibited) drug against morning sickness in pregnant women to the novel and effective anti-myeloma treatment [3].

Wnt-initiated signal transduction cascades play major roles in the control of cell fate, proliferation and migration during developmental stages of organisms but remain relatively silent in healthy adults. Improper re-activation of the Wnt signaling underlies multiple disorders, most notably cancers [4]. These factors make the Wnt-controlled cascades pharmacologically relevant focusing the efforts of many researchers on the development of novel therapies targeting their components.

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